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**WO 01/77087 A1**

(54) Title: NOVEL COMPOUNDS

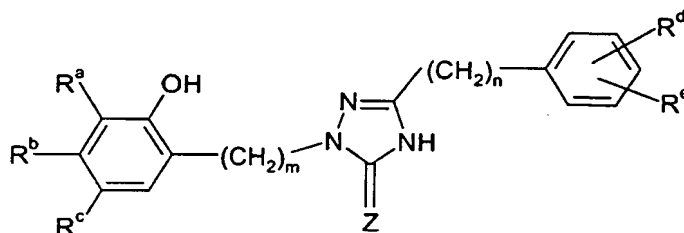
(57) Abstract: The invention provides certain 1,2,4-triazole-3-thione compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

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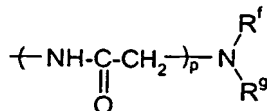
## NOVEL COMPOUNDS

The present invention relates to certain 1,2,4-triazole-3-thione compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

WO 98/04135 discloses a class of substituted triazoles having the general formula



wherein Z is O or S;  $R^a$ ,  $R^b$  and  $R^c$  each are independently selected from hydrogen,



halogen, OH,  $CF_3$ ,  $NO_2$  or

; provided  $R^c$  is not hydrogen; and when  $R^a$  and  $R^b$  are hydrogen,  $R^c$  may be a heterocyclic moiety selected from the group consisting of imidazol-1-yl, morpholinomethyl, N-methylimidazol-2-yl and pyridin-2-yl;  $R^d$  and  $R^e$  each are independently selected from hydrogen, halogen,  $CF_3$ ,  $NO_2$  or imidazol-1-yl; m, n and p each are independently selected from an integer of 0 or 1; and  $R^f$  and  $R^g$  each are independently hydrogen;  $C_1$ - $C_4$  alkyl; or  $R^f$  and  $R^g$ , taken together with the nitrogen atom to which they are attached, is a heterocyclic moiety selected from the group consisting of N-methylpiperazine, morpholine, thiomorpholine, N-benzylpiperazine and imidazolinone. The substituted triazoles are said to act as potassium channel modulators, having application in the treatment of disorders such as ischaemia.

Further substituted triazole compounds having activity at chemokine receptors are disclosed in WO 00/12489.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. At the present time, the chemokine superfamily comprises three groups exhibiting characteristic structural motifs, the C-X-C, C-C and C-X<sub>3</sub>-C families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the

basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X<sub>3</sub>-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues.

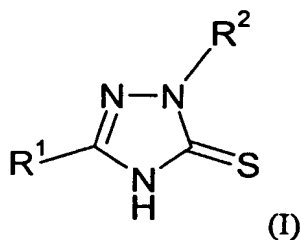
- 5 The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 $\alpha$  and 1 $\beta$  (MIP-1 $\alpha$  and MIP-1 $\beta$ ).

15 The C-X<sub>3</sub>-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX<sub>3</sub>CR1 for the C-X<sub>3</sub>-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

25 In accordance with the present invention, there is therefore provided a compound of general formula



30 in which:

R<sup>1</sup> represents phenyl, naphthyl or a heterocyclic aromatic group containing at least one heteroatom selected from nitrogen, oxygen and sulphur;

R<sup>2</sup> represents a C<sub>1-6</sub> alkylaryl group;

where the aryl group of R<sup>2</sup> and/or the group R<sup>1</sup> is optionally substituted by one or more groups independently selected from halogen, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>6</sub>-alkyl itself optionally substituted by halogen, C(O)R<sup>8</sup>, OR<sup>8</sup>, SR<sup>8</sup>, NR<sup>9</sup>R<sup>10</sup>, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl or phenyl and the

5 aryl group of R<sup>2</sup> and/or the group R<sup>1</sup> is substituted by one or more groups of formula (CH<sub>2</sub>)<sub>n</sub>X(CH<sub>2</sub>)<sub>m</sub>Y;

n and m are independently 0-4;

X is a bond, CO, NR<sup>3</sup>, SO<sub>2</sub>, O or S;

Y is NR<sup>4</sup>COR<sup>5</sup>, CONR<sup>6</sup>R<sup>7</sup>, NR<sup>6</sup>R<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>, OR<sup>8</sup>, SR<sup>8</sup>, NR<sup>8</sup>SO<sub>2</sub>R<sup>8</sup>, SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, COOR<sup>8</sup> or  
10 tetrazol-5-yl;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen, phenyl or C<sub>1</sub>-C<sub>6</sub> alkyl which itself can be optionally substituted by halogen, NO<sub>2</sub>, CN, C<sub>1</sub>-C<sub>6</sub>-alkyl (itself optionally substituted by halogen), C(O)R<sup>8</sup>, OR<sup>8</sup>, SR<sup>8</sup>, NR<sup>9</sup>R<sup>10</sup>, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl or phenyl;

R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, C<sub>3</sub>-C<sub>7</sub> cycloalkyl or phenyl itself optionally  
15 substituted by one or more substituents selected from OR<sup>9</sup>, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl (itself optionally substituted by halogen), pyridinyl, imidazolyl-sulphonyl group, or a C<sub>1</sub>-C<sub>6</sub> alkyl group (itself optionally substituted by one or more groups selected from halogen, OR<sup>8</sup>, COOR<sup>8</sup> or NR<sup>9</sup>R<sup>10</sup>), or R<sup>6</sup> and R<sup>7</sup> together with the nitrogen atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally containing a further  
20 heteroatom selected from nitrogen, oxygen or sulphur and optionally substituted by one or more groups selected from R<sup>8</sup> or NR<sup>9</sup>R<sup>10</sup>;

R<sup>8</sup> is hydrogen, or C<sub>1</sub>-C<sub>6</sub> alkyl or phenyl optionally substituted by halogen; and

R<sup>9</sup> and R<sup>10</sup> are independently hydrogen, phenyl or C<sub>1-6</sub> alkyl itself optionally substituted by halogen or phenyl,

25 and pharmaceutically acceptable salts and solvates thereof.

Examples of 3- to 7-membered heterocyclic rings optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur and optionally substituted by one or more groups selected from R<sup>8</sup> or NR<sup>9</sup>R<sup>10</sup> include pyridine, pyrimidine, thiazole, oxazole,  
30 isoxazole, pyrazole, imidazole, furan and thiophene.

Suitably R<sup>1</sup> represents phenyl, naphthyl or a heterocyclic aromatic group containing at least one heteroatom selected from nitrogen, oxygen and sulphur. Examples of suitable hetrocyclic aromatic groups includes furanyl, thienyl, pyridinyl or pyrimidinyl groups.

35

Preferably R<sup>1</sup> is phenyl substituted as defined above.

More preferably  $R^1$  is phenyl substituted by:

- halogen;
- $(CH_2)_nX(CH_2)_mY$  where  $n$  and  $m$  are 0,  $X$  is a bond and  $Y$  is  $COOR^8$  where  $R^8$  is hydrogen or  $C_1$ - $C_6$  alkyl or  $Y$  is  $SO_2NH_2$  or  $Y$  is  $CONR^6R^7$  where both of  $R^6$  or  $R^7$  are hydrogen  $C_1$ - $C_6$  alkyl or one of  $R^6$  or  $R^7$  is hydrogen and the other is alkyl optionally substituted by hydroxy and/or phenyl,  $NR^9R^{10}$  or hydroxy and  $CO_2Me$ ; or
- $(CH_2)_nX(CH_2)_mY$  where  $n$  and  $m$  are 0,  $X$  is  $CO$  and  $Y$  is  $NHSO_2R^8$  where  $R^8$  is alkyl or phenyl

Most preferably  $R^1$  is phenyl substituted by the substituents exemplified herein, namely: chloro,  $CO_2H$ ,  $CO_2Me$ ,  $CONH_2$ ,  $CONMe_2$ ,  $CONHCH_2CH_2CHMe_2$ ,  $CONHCH(Me)CH(OH)Ph$ ,  $CONHCH_2CH_2OH$ , 3-chloromethyl-1-piperazinylcarbonyl,  $CONHSO_2Me$ ,  $CONHSO_2Ph$ ,  $SO_2NH_2$ ,  $CONHCH(CH_2OH)CO_2Me$ , and  $CONHCH_2C(Me_2)CH_2NMe_2$ ,

Suitably  $R^2$  represents a  $C_{1-6}$  alkylaryl group. Preferably  $R^2$  represents a benzyl group substituted by one or more groups independently selected from halogen or  $(CH_2)_nX(CH_2)_mY$  where  $n$  and  $m$  are 0,  $X$  is a bond and  $Y$  is  $COOR^8$  where  $R^8$  is hydrogen or alkyl or  $Y$  is  $CONR^6R^7$  where one of  $R^6$  or  $R^7$  is hydrogen and the other is alkyl substituted by cyano or halogen. More preferably  $R^2$  represents a benzyl group substituted by halogen,  $CO_2H$ ,  $CO_2Me$ ,  $CONHCH_2CN$  or  $CONHCH_2CH_2F$ . Even more preferably  $R^2$  represents a benzyl group substituted by chloro,  $CO_2H$ ,  $CO_2Me$ ,  $CONHCH_2CN$  or  $CONHCH_2CH_2F$ .

Especially preferred compounds of the invention include:

4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid,

Methyl 4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoate,

4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzamide,

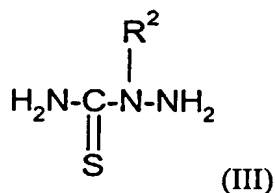
4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N,N*-dimethylbenzamide,

4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N*-(3-methylbutyl)-benzamide,

- [1R, 2S]-4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-benzamide,  
 4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N*-(2-hydroxyethyl)-benzamide,  
 5 2-[(3-Chlorophenyl)methyl]-5-[4-[[4-(3-chlorophenyl)-1-piperazinyl]carbonyl]phenyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione,  
*N*-[4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]benzoyl]-methanesulfonamide,  
*N*-[4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]benzoyl]-  
 10 benzenesulfonamide,  
 2-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid,  
 3-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid,  
 4-[1-[(3-chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-  
 benzenesulfonamide,  
 15 Methyl 2-[(3-)-1-(3-chlorophenyl)methyl-1,2-dihydro-5-thioxo-1*H*[1,2,4]triazol-3-yl))phenylcarbonylamino]-3-hydroxypropanoate,  
 3-{1-[(3-Chlorophenyl)methyl]-1,2-dihydro-5-thioxo-1*H*[1,2,4]triazol-3-yl}-*N*-(2-methyl-2-dimethylaminomethylpropyl)benzamide,  
 3-{1-[(3-Chlorophenyl)methyl]-1,2-dihydro-5-thioxo-1*H*[1,2,4]triazol-3-yl}-*N,N*-  
 20 dimethylbenzamide,  
 {4-[5-(2-Chlorophenyl)-1,2-dihydro-3-thioxo-1*H*-[1,2,4]triazol-2-yl]methyl}-*N*-cyanomethylbenzamide,  
 {4-[5-(2-Chlorophenyl)-1,2-dihydro-3-thioxo-1*H*-[1,2,4]triazol-2-yl]methyl}-*N*-(2-fluoroethyl)benzamide,  
 25 and their pharmaceutically acceptable salts and solvates.

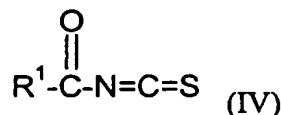
The present invention also provides a process for preparing a compound of formula (I) which comprises:

- (a) reacting a compound of general formula (II),  $R^1-C(O)L$ , wherein L represents a leaving group (such as a halogen atom, e.g. chlorine) and  $R^1$  is as defined in formula (I), with a  
 30 compound of general formula



wherein  $R^2$  is as defined in formula (I), followed by cyclisation; or

(b) reacting a compound of general formula

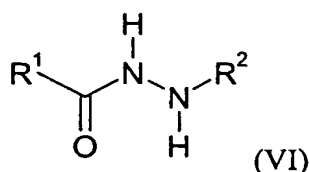


wherein  $\text{R}^1$  is as defined in formula (I), with a compound of general formula



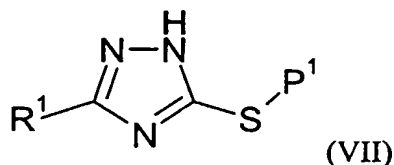
wherein  $\text{R}^2$  is as defined in formula (I), followed by cyclisation; or

(c) reacting a compound of general formula



wherein  $\text{R}^1$  and  $\text{R}^2$  are as defined in formula (I), with ammonium thiocyanate, followed by cyclisation; or

(d) reacting a compound of general formula



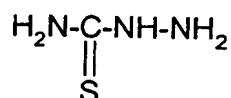
wherein  $\text{P}^1$  represents a protecting group (e.g. methoxyethoxymethyl, triphenylmethyl or ethoxycarbonylethyl) and  $\text{R}^1$  is as defined in formula (I), with a compound of general formula (VIII),  $\text{R}^2-\text{L}^1$ , wherein  $\text{L}^1$  represents a leaving group (e.g. a halogen atom such as bromine, or an alcoholic group under Mitsunobu conditions) and  $\text{R}^2$  is as defined in formula (I), followed by removal of the protecting group  $\text{P}^1$  (e.g. by using suitable acidic or basic conditions);

and optionally after (a), (b), (c) or (d) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

The process of the invention is conveniently carried out in an organic solvent such as dichloromethane, toluene, xylenes, triethylamine, pyridine or tetrahydrofuran at a temperature in the range, e.g. from 10 to 110°C. The cyclisation reaction may be effected under reflux conditions in the presence of sodium hydrogen carbonate, or sodium ethoxide in ethanol as described by H. Behringer *et al.*, *Liebigs Ann. Chem.*, 1975, 1264-1271.

Compounds of formula (II), (III), (IV), (V), (VI) and (VIII) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

- 5 Compounds of formula (VII) may be prepared by a process analogous to that of step (a) above using the compound

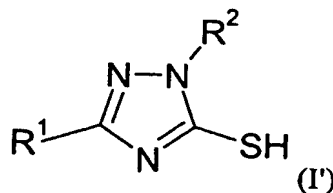


in place of the compound of formula (III).

- 10 It will be appreciated by those skilled in the art that in the processes described above the functional groups (e.g. hydroxyl groups) of intermediate compounds may need to be protected by protecting groups. The final stage in the preparation of the compounds of the invention may involve the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic  
15 Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1991).

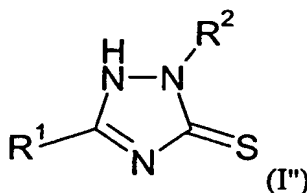
- 20 The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an ammonium salt or an alkali metal salt such as a sodium or potassium salt.

- 25 Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention, particularly tautomers of general formula



or





wherein R<sup>1</sup> and R<sup>2</sup> are as defined in formula (I) above.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CXCR2) activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

- (1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;
- (2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;
- (3) **(skin)** psoriasis, atopic dermatitis, contact dermatitis and other eczematous dermatides, seborrhectic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;
- (4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders, e.g. Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal disorders, e.g. tropical spastic paraparesis, and stiff-man syndrome; paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia purpura; post-operative adhesions, and sepsis.

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Cancers, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, and tumour metastasis;

(9) Diseases in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC, diabetic retinopathy).

(10) Cystic fibrosis, re-perfusion injury in the heart, brain, peripheral limbs and other organs.

(11) Burn wounds & chronic skin ulcers

(12) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and  
implantation, Pre-term labour, Endometriosis)

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CXC chemokine receptor subfamily, more preferably the target chemokine receptor is the CXCR2 receptor.

Particular conditions which can be treated with the compounds of the invention are psoriasis, diseases in which angiogenesis is associated with raised CXCR2 chemokine levels, and COPD. It is preferred that the compounds of the invention are used to treat psoriasis.

As a further aspect of the present invention, certain compounds of formula (I) may have utility as antagonists of the CX3CR1 receptor. Such compounds are expected to be particularly useful in the treatment of disorders within the central and peripheral nervous system and other conditions characterized by an activation of microglia and/or infiltration of leukocytes (e.g. stroke/ischemia and head trauma).

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial, in particular modulation of the CXCR2 receptor.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

5 The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CXCR2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

10 The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

15 For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

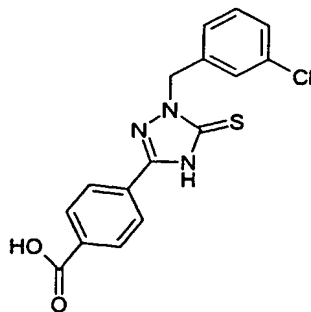
20 The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably  
25 comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

30 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

35 The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compounds of the invention are administered orally.

The invention will now be further illustrated by reference to the following examples. In the examples the Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer and the Mass Spectrometry (MS) spectra measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer. Where necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Chromatography was generally performed using Matrex Silica 60<sup>®</sup> (35-70 micron) or Prolabo Silica gel 60<sup>®</sup> (35-70 micron) suitable for flash silica gel chromatography. High pressure liquid chromatography purification was performed using either a Waters Micromass LCZ with a Waters 600 pump controller, Waters 2487 detector and Gilson FC024 fraction collector or a Waters Delta Prep 4000. The abbreviations m.p. and DMSO used in the examples stand for melting point and dimethyl sulphoxide respectively.

**Example 1****4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]-benzoic acid****i) 2-(3-Chlorophenyl)methyl thiosemicarbazide**

(3-Chlorophenyl)methylhydrazine hydrochloride ( 50.0g) and ammonium thiocyanate (19.8g) were heated at reflux in ethanol (200ml) overnight. The hot suspension was filtered and the filtrate was allowed to cool and crystallize. The crystals were removed and dried to give the subtitle compound as colourless needles (27.6g)

m.p.: 153-158°C

MS: ESI(+ve) 216 (M+1, 100%)

<sup>1</sup>H NMR: δ (DMSO) 7.65 (br, 2H), 7.42-7.27 (m, 4H), 5.22 (s, 2H), 4.75 (s, 2H)

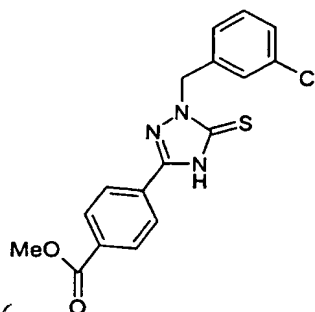
**ii) 4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]-benzoic acid**

Monomethyl terephthalate (1.67g) and thionyl chloride (20ml) were heated together at reflux for 1 hour, then concentrated *in-vacuo* to give a solid which was dissolved in pyridine (30ml) and treated with the product from step (i) (2.00g). The mixture was stirred for 3.5 hours then concentrated *in-vacuo* to remove the pyridine. The residue was suspended in 2M sodium hydroxide (30ml) and heated at reflux for 5 hours. After allowing to cool overnight, the mixture was filtered to remove solids and washed with diethyl ether. The aqueous solution was acidified with 2M hydrochloric acid to give a precipitate which was removed by filtration and dried to give the title compound as a white powder (2.78g).

m.p.: 302°C

MS: ESI(-ve) 344 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.34 (br, 1H), 13.26 (br, 1H), 8.01-8.08 (m, 4H), 7.33-7.47 (m, 4H), 5.42 (s, 2H).

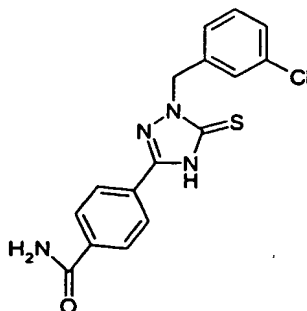
**Example 2****Methyl 4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]-benzoate**

A suspension of the product from Example 1 step (ii) (0.20g) in thionyl chloride (5ml) was heated at reflux for 1 hour then concentrated *in-vacuo*. The residue was dissolved in tetrahydrofuran (5ml) and methanol (1ml) and stirred overnight. After concentration *in-vacuo* the crude product was purified by chromatography eluting with 3% methanol in dichloromethane followed by recrystallisation from ethyl acetate. Yield 0.023g.

m.p.: 263.5-264.5°C

MS: APCI(-ve) 358 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.35 (br, 1H), 8.04-8.07 (m, 4H), 7.35-7.46 (m, 4H), 5.41 (s, 2H), 3.88 (s, 3H).

**Example 3****4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]-benzamide**

Prepared by the method of Example 2 using '880' aqueous ammonia instead of methanol.

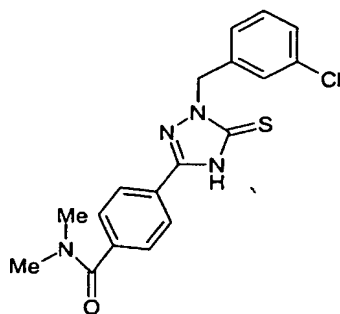
m.p.: 310-312°C

MS: APCI(-ve) 343 (M-1, 100%).

<sup>1</sup>H NMR:  $\delta$  (DMSO) 14.27 (br, 1H), 8.09 (br, 1H), 7.97-8.02 (m, 4H), 7.52 (br, 1H), 7.34-7.46 (m, 4H), 5.41 (s, 2H).

5 **Example 4**

**4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N,N*-dimethyl-benzamide**



10

Prepared by the method of Example 2 using 2M dimethylamine solution in tetrahydrofuran instead of methanol.

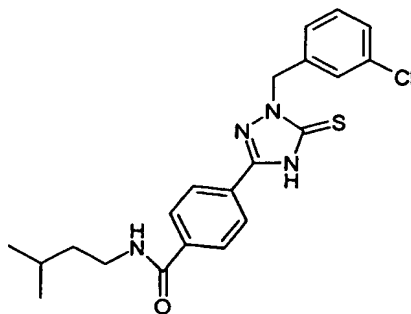
m.p.: 302-304°C

15 MS: APCI(-ve) 371 (M-1, 100%).

<sup>1</sup>H NMR:  $\delta$  (DMSO) 14.26 (br, 1H), 7.96 (d, 2H), 7.54 (d, 2H), 7.32-7.46 (m, 4H), 5.41 (s, 2H), 2.99 (br, 3H), 2.90 (br, 3H).

**Example 5**

20 **4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N*-(3-methylbutyl)-benzamide**





A suspension of the product from Example 1 step (ii) (0.25g) in thionyl chloride (3.3ml) was heated at reflux for 1 hour then concentrated *in-vacuo*. The residue was dissolved in tetrahydrofuran (5ml) and treated with N,N-diisopropylethylamine (0.63ml) followed by isoamylamine (0.17ml). The mixture was stirred for 2 days, then concentrated *in-vacuo*.

The crude product was purified by chromatography eluting with 2% methanol in dichloromethane, then by chromatography eluting with 33% ethyl acetate in isohexane, and finally by trituration with diethyl ether to give the title compound as a pale brown solid (0.023g).

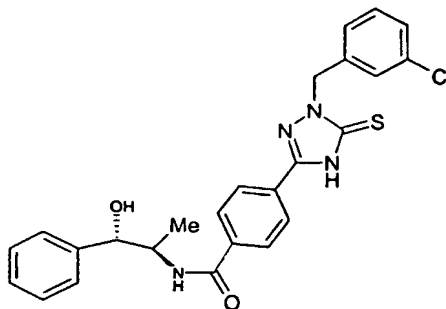
m.p.: 218-220°C

MS: ESI(-ve) 413 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.26 (br, 1H), 8.54 (t, 1H), 7.93-8.00 (m, 4H), 7.32-7.45 (m, 4H), 5.41 (s, 2H), 3.25-3.32 (m, 2H), 1.58-1.64 (m, 1H), 1.39-1.46 (m, 2H), 0.90 (d, 6H).

#### Example 6

[1R, 2S]-4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]-N-(2-hydroxy-1-methyl-2-phenylethyl)-benzamide



Prepared by the method of Example 7 using D-(+)-norephedrine instead of isoamylamine.

m.p.: 220-222°C

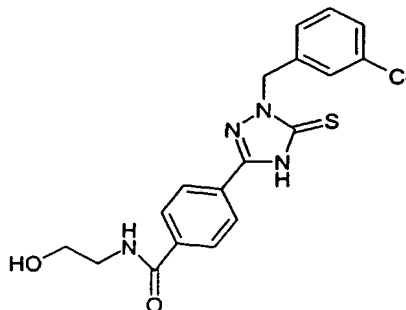
MS: ESI(-ve) 477 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.25 (br, 1H), 8.34 (d, 1H), 7.88-7.97 (m, 4H), 7.17-7.45 (m, 9H), 5.41-5.45 (m, 3H), 4.70 (t, 1H), 4.12-4.18 (m, 1H), 1.11 (d, 3H).

**Example 7**

**4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]-N-(2-hydroxyethyl)-benzamide**

5



A suspension of the product from Example 1 step (ii) (0.20g) in tetrahydrofuran (5ml) was treated with 1,1'-carbonyldiimidazole (0.11g) and stirred for 1.5 hours. Ethanolamine (0.070ml) was added and the mixture was stirred overnight then concentrated *in-vacuo*. The crude product was purified by chromatography eluting with 5% methanol in dichloromethane and then by trituration with diethyl ether to give the title compound as a white powder (0.075g).

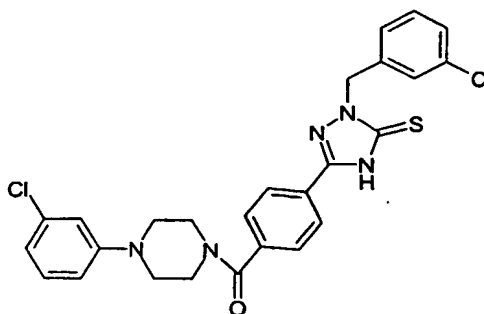
15 m.p.: 188-190°C

MS: ESI(+ve) 389 (M+1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 8.56 (t, 1H), 7.98 (br, 4H), 7.33-7.46 (m, 4H), 5.41 (s, 2H), 3.52 (t, 2H), 3.32-3.37 (m, 2H).

20 **Example 8**

**2-[(3-Chlorophenyl)methyl]-5-[4-[[4-(3-chlorophenyl)-1-piperazinyl]carbonyl]phenyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione**



Prepared by the method of Example 7 using N,N-diisopropylethylamine and 1-(3-chlorophenyl)piperazine dihydrochloride instead of ethanolamine.

5 m.p.: 260-262°C

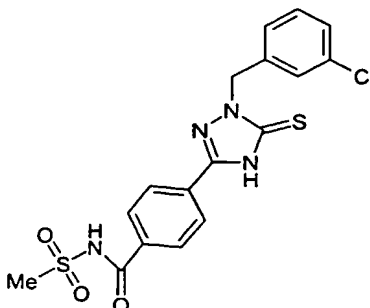
MS: ESI(+ve) 524 (M+1, 100%).

<sup>1</sup>H NMR: δ (DMSO at 90°) 13.93 (br, 1H), 7.97 (d, 2H), 7.56 (d, 2H), 7.33-7.44 (m, 4H), 7.20 (t, 1H), 6.92 (s, 1H), 6.87 (d, 1H), 6.79 (d, 1H), 5.39 (s, 2H), 3.61 (br, 4H), 3.24 (br, 4H).

10

### Example 9

N-[4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]benzoyl]-methanesulfonamide



15

The product from Example 1 step (ii) (0.20g), methanesulphonamide (0.062g), N,N-dimethylaminopyridine (0.078g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.125g) were stirred together in dichloromethane (10ml) for 6 days. The mixture was concentrated *in-vacuo* and the crude product was purified by chromatography eluting with 70% acetonitrile in dichloromethane followed by preparative reversed-phase HPLC ( Waters Symmetry C<sub>8</sub> eluted with a gradient of 0.1% aqueous ammonium acetate buffer and acetonitrile). Lyophilisation gave the title compound as an amorphous solid (0.043g).

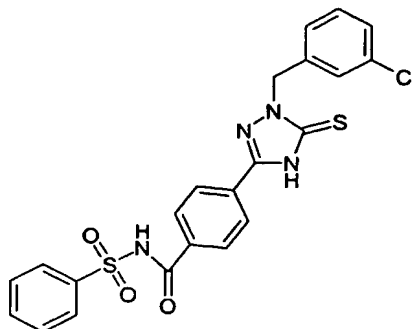
20

25 MS: APCI(-ve) 421 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 8.04 (d, 2H), 7.93 (d, 2H), 7.33-7.46 (m, 4H), 5.41 (s, 2H), 3.05 (s, 3H).

**Example 10**

***N*-[4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]benzoyl]-benzenesulfonamide**



5

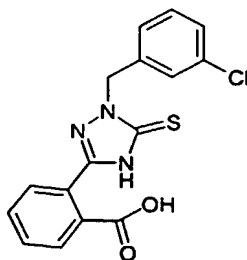
Prepared by the method of Example 9 using phenylsulphonamide instead of methanesulphonamide and heating the mixture at reflux for 2 days.

10 MS: APCI(-ve) 483 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.27 (br, 1H), 7.96-8.00 (m, 6H), 7.57-7.67 (m, 3H), 7.32-7.46 (m, 4H), 5.40 (s, 2H).

15 **Example 11**

**2-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid**



20 Prepared by the method of Example 1 step (ii) using methyl hydrogen phthalate instead of monomethylterephthalate.

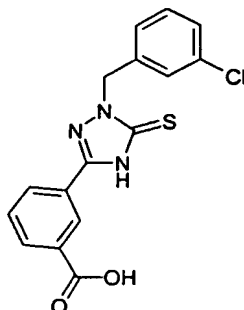
m.p.: 234-238°C

MS: APCI(-ve) 344 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 13.82 (br, 1H), 13.22 (br, 1H), 7.93-7.98 (m, 1H), 7.65-7.74 (m, 2H), 7.58-7.63 (m, 1H), 7.36-7.43 (m, 3H), 7.26-7.31 (m, 1H), 5.37 (s, 2H).

### Example 12

5 3-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid



Prepared by the method of Example 1 step (ii) using monomethyl isophthalate instead of  
10 monomethyl terephthalate.

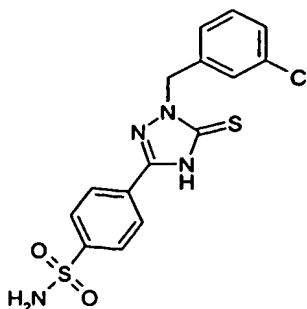
m.p.: 314-316°C

MS: APCI(-ve) 344 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.33 (br, 1H), 13.29 (br, 1H), 8.52 (s, 1H), 8.14 (d, 1H), 8.07 (d,  
15 1H), 7.66 (t, 1H), 7.34-7.47 (m, 4H), 5.41 (s, 2H).

### Example 13

4-[1-[(3-chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-  
benzenesulfonamide



Prepared by the method of Example 1 step (ii) using 4-carboxybenzenesulfonamide  
instead of monomethyl terephthalate.

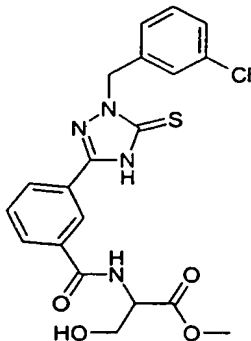
m.p.: 281-283°C

MS: ESI(-ve) 379 (M-1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.34 (br, 1H), 8.07 (d, 2H), 7.93 (d, 2H), 7.33-7.50 (m, 6H), 5.41 (s, 2H).

#### Example 14

**Methyl 2-[(3-)-1-(3-chlorophenyl)methyl-1,2-dihydro-5-thioxo-1H[1,2,4]triazol-3-yl)]phenylcarbonylamino]-3-hydroxypropanoate**



A solution of 3-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1H-1,2,4-triazol-3-yl]-benzoic acid (0.20g) in dry tetrahydrofuran (5ml) was stirred under nitrogen with 1,1'-carbonyldiimidazole (0.104g) for 1 hour. DL-Serine methyl ester hydrochloride (0.109g) and diethylisopropylamine (0.15mL) were added and the mixture stirred 18 hours. The mixture was absorbed onto silica and purified by chromatography (dichloromethane: methanol, 97:3) to give the title compound (0.069g).

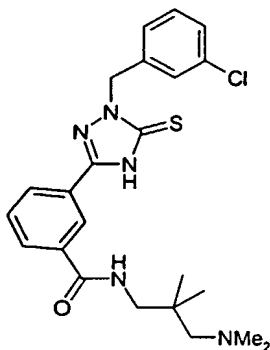
m.p.: 188-196°C

MS: APCI(+ve) 447 (M+1, 100%).

<sup>1</sup>H NMR: δ (DMSO) 14.28 (s, 1H), 8.73 (d, 1H), 8.41 (s, 1H), 8.07 (d, 1H), 8.02 (d, 1H), 7.65 (t, 1H), 7.44 (m, 1H), 7.34 (m, 2H), 5.42 (s, 2H), 5.08 (t, 1H), 4.57 (q, 1H), 3.80 (t, 2H), 3.66 (s, 3H).

**Example 15**

**3-{1-[(3-Chlorophenyl)methyl]-1,2-dihydro-5-thioxo-1H[1,2,4]triazol-3-yl}-N-(2-methyl-2-dimethylaminomethylpropyl)benzamide**



Prepared by the method of Example 15 using N,N,2,2-tetramethyl-1,3-propanediamine (0.222mL) to give the title compound as a solid (0.046g)

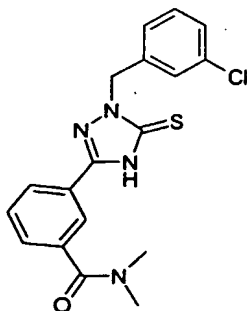
m.p.: 173-175°C

MS: APCI(+ve) 458 (M+1,100%).

<sup>1</sup>H NMR: δ (DMSO) 8.77 (t, 1H), 8.32 (s, 1H), 8.03 (d, 1H), 7.90 (d, 1H), 7.60 (t, 1H), 7.43 (s, 1H), 7.36 (m, 2H), 7.32 (m, 1H), 5.40 (s, 2H), 3.21 (d, 2H), 2.37 (s, 8H), 30.92 (s, 6H).

**Example 16**

**3-{1-[(3-Chlorophenyl)methyl]-1,2-dihydro-5-thioxo-1H[1,2,4]triazol-3-yl}-N,N-dimethylbenzamide**



Prepared by the method of Example 15 using dimethylamine (1.4mL of 2M in tetrahydrofuran) to give the title compound as a solid (0.039g)

m.p.: 184-187°C

MS: APCI(+ve) 373 (M+1,100%).

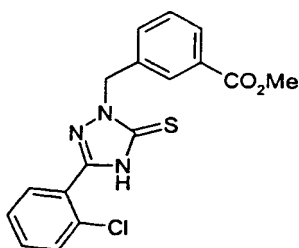
<sup>1</sup>H NMR: δ (DMSO) 14.22 (s, 1H), 7.95 (m, 2H), 7.56 (m, 2H), 7.44 (s,1H), 7.35 (m, 3H), 5.40 (s, 2H), 3.00 (s, 3H), 2.92 (s, 3H).

5 **Example 17**

**{4-[5-(2-Chlorophenyl)-1,2-dihydro-3-thioxo-1H-[1,2,4]triazol-2-yl)methyl]-N-cyanomethylbenzamide**

**(a) Methyl 3-[5-(2-chlorophenyl)-1,2-dihydro-3-thioxo-1H-[1,2,4]triazol-2-yl)methyl]benzoate**

10



5-(2-Chlorophenyl)-3-triphenylmethylthio-1H-1,2,4-triazole (10g), potassium carbonate (2.8g) and methyl 3-bromomethylbenzoate (4.2g) were stirred together in dry DMF (20ml) for 5hrs. Water was added and the mixture extracted with dichloromethane. The extracts were washed with saturated sodium chloride solution then dried and filtered. Trifluoroacetic acid (2ml) was added and the solution stood 10mins. The solution was evaporated under reduced pressure. Purification was by chromatography eluting with 2% ethyl acetate in dichloromethane to give a solid (2.4g). A sample (0.25g) was further purified under the same conditions to give a solid which was triturated with ether to give a solid which was collected and dried. Yield 0.062g

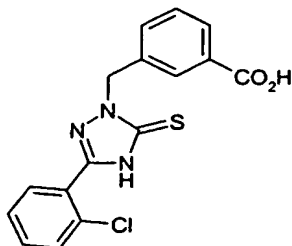
m.p.: 161-162°C

MS: APCI(+ve): 360 (M+1), 328 (100%)

25 <sup>1</sup>H NMR: δ (DMSO) 14.05 (bs, 1H), 7.98 (s, 1H), 7.91 (d, 1H), 7.64 (m, 3H), 7.53 (m, 3H), 5.47 (s, 2H), 3.85 (s, 3H).



**(b) 3-[5-(2-chlorophenyl)-1,2-dihydro-3-thioxo-1H-[1,2,4]triazol-2-ylmethyl]benzoic acid**



5 A solution of lithium hydroxide monohydrate (0.49g) in water (50ml) was added to a solution of methyl 3-[5-(2-chlorophenyl)-1,2-dihydro-3-thioxo-1H-[1,2,4]triazol-2-ylmethyl]benzoate (2.1g) in methanol (150ml) and the mixture stirred 18hrs. The mixture was concentrated in vacuo and the residue taken up in water with sodium hydroxide solution (2ml of 2M). The resulting solution was filtered and acidified with dilute  
10 hydrochloric acid. The solid which separated was collected by filtration, washed with water and air dried. Purification was by chromatography eluting with 5% methanol in dichloromethane to give a solid (1.1g). The more pure fractions were collected, concentrated in vacuo to give a solid which was triturated with ether and collected then dried to give a solid (0.10g).

15

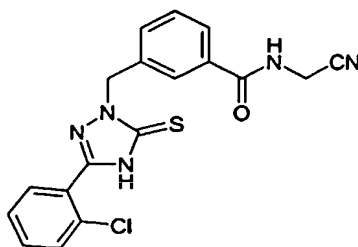
m.p.: 257-261°C

MS: APCI(+ve): 346 (M+1, 100%)

<sup>1</sup>H NMR: δ (DMSO) 14.04 (bs, 1H), 13.03 (bs, 1H), 7.96 (s, 1H), 7.89 (d, 1H), 7.60 (m, 3H), 7.50 (m, 2H), 5.46 (s, 2H).

20

**{4-[5-(2-Chlorophenyl)-1,2-dihydro-3-thioxo-1H-[1,2,4]triazol-2-yl]methyl}-N-cyanomethylbenzamide**



25

3-[5-(2-chlorophenyl)-1,2-dihydro-3-thioxo-1H-[1,2,4]triazol-2-ylmethyl]benzoic acid (0.346g) was stirred in dichloromethane (3ml) with oxalyl chloride (0.131ml) and dry dimethylformamide (2drops) for 3hrs. The resulting solution was concentrated in vacuo then redissolved in dichloromethane (1ml) and added to a suspension of aminoacetonitrile hydrochloride (0.111g) and triethylamine (0.35ml) in dichloromethane (2ml). The mixture was stirred 18hrs. The mixture was diluted with dichloromethane and extracted into sodium bicarbonate solution. The aqueous was acidified with dilute hydrochloric acid and extracted into dichloromethane. The extracts were washed with saturated sodium chloride solution then dried and evaporated. Purification was by chromatography eluting with 30% ethyl acetate in dichloromethane to give a solid which was slurried with ether and collected to leave a solid (0.019g).

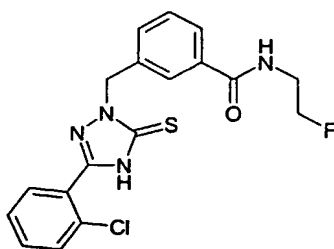
m.p.: 178-182°C

MS: APCI(+ve): 384 (M+1,100%)

<sup>1</sup>H NMR: δ (DMSO) 14.04 (s, 1H), 9.24 (t, 1H), 7.88 (s, 1H), 7.80 (d, 1H), 7.67 (m, 2H), 7.50 (m, 4H), 5.45 (s, 2H), 4.31 (d, 2H).

#### EXAMPLE 18

{4-[5-(2-Chlorophenyl)-1,2-dihydro-3-thioxo-1H-[1,2,4]triazol-2-yl]methyl}-N-(2-fluoroethyl)benzamide



25

Prepared by the method of Example 20 using 2-fluoroethylamine hydrochloride (0.119g) to give the title compound as a solid (0.053g)

m.p.: 165-168°C

MS: APCI(+ve) 391 (M+1,100%).

<sup>1</sup>H NMR: δ (DMSO) 14.03 (s, 1H), 8.73 (t, 1H), 7.88 (s, 1H), 7.80 (d, 1H), 7.66 (m, 2H), 7.58 (td, 1H), 7.50 (m, 4H), 5.44 (s, 2H), 4.61 (t, 1H), 4.45 (t, 1H), 3.60 (q, 1H), 3.51 (q, 1H).

## 5 Pharmacological Data

### Ligand Binding Assay

[<sup>125</sup>I]IL-8 (human, recombinant) was purchased from Amersham, U.K. with a specific activity of 2,000Ci/mmol. All other chemicals were of analytical grade. High levels of hrCXCR2 were expressed in HEK 293 cells (human embryo kidney 293 cells ECACC No. 85120602) (Lee *et al.* (1992) *J. Biol. Chem.* **267** pp16283-16291). hrCXCR2 cDNA was amplified and cloned from human neutrophil mRNA. The DNA was cloned into PCRScript (Stratagene) and clones were identified using DNA. The coding sequence was sub-cloned into the eukaryotic expression vector RcCMV (Invitrogen). Plasmid DNA was prepared using Quiagen Megaprep 2500 and transfected into HEK 293 cells using Lipofectamine reagent (Gibco BRL). Cells of the highest expressing clone were harvested in phosphate-buffered saline containing 0.2%(w/v) ethylenediaminetetraacetic acid (EDTA) and centrifuged (200g, 5min.). The cell pellet was resuspended in ice cold homogenisation buffer [10mM HEPES (pH 7.4), 1mM dithiothreitol, 1mM EDTA and a panel of protease inhibitors (1mM phenyl methyl sulphonyl fluoride, 2µg/ml soybean trypsin inhibitor, 3mM benzamidine, 0.5µg/ml leupeptin and 100µg/ml bacitracin)] and the cells left to swell for 10 minutes. The cell preparation was disrupted using a hand held glass mortar/PTFE pestle homogeniser and cell membranes harvested by centrifugation (45 minutes, 100,000g, 4°C). The membrane preparation was stored at -70°C in homogenisation buffer supplemented with Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH<sub>2</sub>PO<sub>4</sub>), 0.1%(w/v) gelatin and 10%(v/v) glycerol.

All assays were performed in a 96-well MultiScreen 0.45µm filtration plates (Millipore, U.K.). Each assay contained ~33pM [<sup>125</sup>I]IL-8 and membranes (equivalent to ~80,000 cells) in assay buffer [Tyrode's salt solution supplemented with 10mM HEPES (pH 7.4), 1.8mM CaCl<sub>2</sub>, 1mM MgCl<sub>2</sub>, 0.5mg/ml bacitracin and 0.1%(w/v) gelatin]. In addition, a compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to reach a final concentration of 1%(v/v) DMSO. The assay was initiated with the addition of membranes and after 1.5 hours at room temperature the membranes were harvested by filtration using a Millipore MultiScreen vacuum manifold and washed twice with assay buffer (without bacitracin). The backing plate was removed from the

MultiScreen plate assembly, the filters dried at room temperature, punched out and then counted on a Cobra  $\gamma$ -counter.

5 The compounds of formula (I) according to the Examples were found to have  $IC_{50}$  values of less than ( $<$ )  $10\mu M$ .

#### **Intracellular Calcium Mobilisation Assay**

Human neutrophils were prepared from EDTA-treated peripheral blood, as previously described (Baly *et al.* (1997) *Methods in Enzymology* 287 pp70-72), in storage buffer  
10 [Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM  $NaH_2PO_4$ ) supplemented with 5.7mM glucose and 10mM HEPES (pH 7.4)].

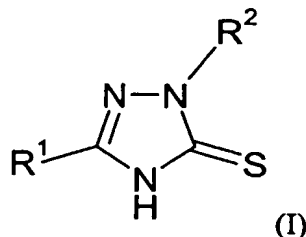
The chemokine GRO $\alpha$  (human, recombinant) was purchased from R&D Systems (Abingdon, U.K.). All other chemicals were of analytical grade. Changes in intracellular  
15 free calcium were measured fluorometrically by loading neutrophils with the calcium sensitive fluorescent dye, fluo-3, as described previously (Merritt *et al.* (1990) *Biochem. J.* 269, pp513-519). Cells were loaded for 1 hour at 37°C in loading buffer (storage buffer with 0.1%(w/v) gelatin) containing 5 $\mu M$  fluo-3 AM ester, washed with loading buffer and then resuspended in Tyrode's salt solution supplemented with 5.7mM glucose, 0.1%(w/v)  
20 bovine serum albumin (BSA), 1.8mM  $CaCl_2$  and 1mM  $MgCl_2$ . The cells were pipetted into black walled, clear bottom, 96 well micro plates (Costar, Boston, U.S.A.) and centrifuged (200g, 5 minutes, room temperature).

A compound of formula (I) according to the Examples was pre-dissolved in DMSO and  
25 added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an  $A_{50}$  concentration of GRO $\alpha$  and the transient increase in fluo-3 fluorescence ( $\lambda_{Ex}$  =490nm and  $\lambda_{Em}$  = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

30 The compounds of formula (I) according to the Examples were tested and found to be antagonists of the CXCR2 receptor in human neutrophils.

## CLAIMS

1. A compound of general formula



in which:

$R^1$  represents phenyl, naphthyl or a heterocyclic aromatic group containing at least one heteroatom selected from nitrogen, oxygen and sulphur;

$R^2$  represents a  $C_{1-6}$  alkylaryl group;

where the aryl group of  $R^2$  and/or the group  $R^1$  is optionally substituted by one or more groups independently selected from halogen,  $NO_2$ , CN,  $C_1-C_6$ -alkyl itself optionally substituted by halogen,  $C(O)R^8$ ,  $OR^8$ ,  $SR^8$ ,  $NR^9R^{10}$ ,  $C_3-C_7$ -cycloalkyl or phenyl and the aryl group of  $R^2$  and/or the group  $R^1$  is substituted by one or more groups of formula  $(CH_2)_nX(CH_2)_mY$ ;

n and m are independently 0-4;

X is a bond, CO,  $NR^3$ ,  $SO_2$ , O or S;

Y is  $NR^4COR^5$ ,  $CONR^6R^7$ ,  $NR^6R^7SO_2R^8$ ,  $OR^8$ ,  $SR^8$ ,  $NR^8SO_2R^8$ ,  $SO_2NR^6R^7$ ,  $COOR^8$  or tetrazol-5-yl;

$R^3$ ,  $R^4$  and  $R^5$  are independently hydrogen, phenyl or  $C_1-C_6$  alkyl which itself can be optionally substituted by halogen,  $NO_2$ , CN,  $C_1-C_6$ -alkyl (itself optionally substituted by halogen),  $C(O)R^8$ ,  $OR^8$ ,  $SR^8$ ,  $NR^9R^{10}$ ,  $C_3-C_7$ -cycloalkyl or phenyl;

$R^6$  and  $R^7$  are independently hydrogen,  $C_3-C_7$  cycloalkyl or phenyl itself optionally substituted by one or more substituents selected from  $OR^9$ , halogen,  $C_1-C_6$  alkyl (itself optionally substituted by halogen), pyridinyl, imidazolyl-sulphonyl group, or a  $C_1-C_6$  alkyl group (itself optionally substituted by one or more groups selected from halogen,  $OR^8$ ,  $COOR^8$  or  $NR^9R^{10}$ ), or  $R^6$  and  $R^7$  together with the nitrogen atom to which they are attached form a 3- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulphur and optionally substituted by one or more groups selected from  $R^8$  or  $NR^9R^{10}$ ;

$R^8$  is hydrogen, or  $C_1-C_6$  alkyl or phenyl optionally substituted by halogen; and

$R^9$  and  $R^{10}$  are independently hydrogen, phenyl or  $C_{1-6}$  alkyl itself optionally substituted by halogen or phenyl,

and pharmaceutically acceptable salts and solvates thereof.

2. A compound according to claim 1, wherein  $R^1$  is phenyl substituted as defined in claim 1

3. A compound according to claim 1 or 2 wherein  $R^1$  is phenyl substituted by:  
halogen;

$(CH_2)_nX(CH_2)_mY$  where  $n$  and  $m$  are 0,  $X$  is a bond and  $Y$  is  $COOR^8$  where  $R^8$  is hydrogen or  $C_1-C_6$  alkyl or  $Y$  is  $SO_2NH_2$  or  $Y$  is  $CONR^6R^7$  where both of  $R^6$  or  $R^7$  are hydrogen or  $C_1-C_6$  alkyl or one of  $R^6$  or  $R^7$  is hydrogen and the other is alkyl optionally substituted by hydroxy and/or phenyl,  $NR^9R^{10}$  or hydroxy and  $CO_2Me$ ; or

$(CH_2)_nX(CH_2)_mY$  where  $n$  and  $m$  are 0,  $X$  is  $CO$  and  $Y$  is  $NHSO_2R^8$  where  $R^8$  is alkyl or phenyl.

4. A compound according to claim 1 or 2 wherein  $R^1$  is phenyl substituted by chloro,  $CO_2H$ ,  $CO_2Me$ ,  $CONH_2$ ,  $CONMe_2$ ,  $CONHCH_2CH_2CHMe_2$ ,  $CONHCH(Me)CH(OH)Ph$ ,  $CONHCH_2CH_2OH$ , 3-chloromethyl-1-piperazinylcarbonyl,  $CONHSO_2Me$ ,  $CONHSO_2Ph$ ,  $SO_2NH_2$ ,  $CONHCH(CH_2OH)CO_2Me$  or  $CONHCH_2C(Me_2)CH_2NMe_2$ .

5. A compound according to any one of claims 1 to 4 wherein  $R^2$  represents a benzyl group substituted by one or more groups independently selected from halogen or  $(CH_2)_nX(CH_2)_mY$  where  $n$  and  $m$  are 0,  $X$  is a bond and  $Y$  is  $COOR^8$  where  $R^8$  is hydrogen or alkyl or  $Y$  is  $CONR^6R^7$  where one of  $R^6$  or  $R^7$  is hydrogen and the other is alkyl substituted by cyano or halogen.

6. A compound according to any one of claims 1 to 4 wherein  $R^2$  represents a benzyl group substituted by halogen,  $COOH$ ,  $COOMe$ ,  $CONHCH_2CN$  or  $CONHCH_2CH_2F$ .

7. A compound according to any one of claims 1 to 6 selected from:

4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid,  
Methyl 4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoate,

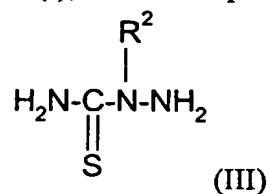
4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzamide,

4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N,N*-dimethylbenzamide,

- 4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N*-(3-methylbutyl)-benzamide,  
 [1*R*, 2*S*]-4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-benzamide,  
 5 4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-*N*-(2-hydroxyethyl)-benzamide,  
 2-[(3-Chlorophenyl)methyl]-5-[4-[[4-(3-chlorophenyl)-1-piperazinyl]carbonyl]phenyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione,  
*N*-[4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]benzoyl]-  
 10 methanesulfonamide,  
*N*-[4-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]benzoyl]-benzenesulfonamide,  
 2-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid,  
 3-[1-[(3-Chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzoic acid,  
 15 4-[1-[(3-chlorophenyl)methyl]-4,5-dihydro-5-thioxo-1*H*-1,2,4-triazol-3-yl]-benzenesulfonamide,  
 Methyl 2-[(3-)-1-(3-chlorophenyl)methyl-1,2-dihydro-5-thioxo-1*H*[1,2,4]triazol-3-yl))phenylcarbonylamino]-3-hydroxypropanoate,  
 3-{1-[(3-Chlorophenyl)methyl]-1,2-dihydro-5-thioxo-1*H*[1,2,4]triazol-3-yl}-*N*-(2-methyl-  
 20 2-dimethylaminomethylpropyl)benzamide,  
 3-{1-[(3-Chlorophenyl)methyl]-1,2-dihydro-5-thioxo-1*H*[1,2,4]triazol-3-yl}-*N,N*-dimethylbenzamide,  
 {4-[5-(2-Chlorophenyl)-1,2-dihydro-3-thioxo-1*H*-[1,2,4]triazol-2-yl]methyl}-*N*-cyanomethylbenzamide,  
 25 {4-[5-(2-Chlorophenyl)-1,2-dihydro-3-thioxo-1*H*-[1,2,4]triazol-2-yl]methyl}-*N*-(2-fluoroethyl)benzamide,  
 and their pharmaceutically acceptable salts and solvates.

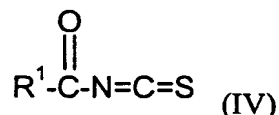
8. A process for preparing a compound of formula (I) as defined in claim 1 which  
 30 comprises:

(a) reacting a compound of general formula (II),  $R^1-C(O)L$ , wherein *L* represents a leaving group and  $R^1$  is as defined in formula (I), with a compound of general formula

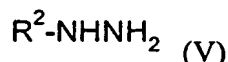


wherein  $R^2$  is as defined in formula (I), followed by cyclisation; or

(b) reacting a compound of general formula

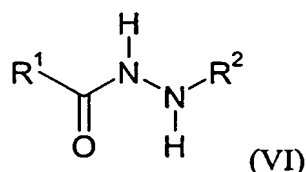


wherein  $R^1$  is as defined in formula (I), with a compound of general formula



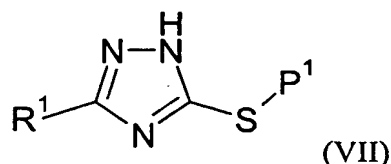
wherein  $R^2$  is as defined in formula (I), followed by cyclisation; or

(c) reacting a compound of general formula



wherein  $R^1$  and  $R^2$  are as defined in formula (I), with ammonium thiocyanate, followed by cyclisation; or

(d) reacting a compound of general formula



wherein  $P^1$  represents a protecting group and  $R^1$  is as defined in formula (I), with a compound of general formula (VIII),  $R^2-L^1$ , wherein  $L^1$  represents a leaving group and  $R^2$  is as defined in formula (I), followed by removal of the protecting group  $P^1$ ;

and optionally after (a), (b), (c) or (d) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I).

9. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.



11. A compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 for use in therapy.
12. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in therapy.
13. A method of treating a chemokine mediated disease wherein the chemokine binds to a one or more chemokine receptors, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 7.
14. A method according to claim 13 in which the chemokine receptor belongs to the CXC chemokine receptor subfamily.
15. A method according to claim 13 or 14 in which the chemokine receptor is the CXCR2 receptor.
16. A method according to claims 13 to 15 wherein the disease is psoriasis, a disease in which angiogenesis is associated with raised CXCR2 chemokine levels, or COPD.
17. A method according to claim 16, wherein the disease is psoriasis.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00753

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 249/12, C07D 401/04, C07D 405/04, C07D 409/04, A61K 31/4196,  
A61P 11/00, A61P 17/06, A61P 25/00 A61P 19/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0012489 A1 (ASTRA PHARMACEUTICALS LTD.), 9 March 2000 (09.03.00)	1-17
	--	
X	WO 9804135 A1 (BRISTOL-MYERS SQUIBB COMPANY), 5 February 1998 (05.02.98)	1-7,9-12
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 August 2001

Date of mailing of the international search report

09 -08- 2001

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE01/00753

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **13-17**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE01/00753

Claims 13-17 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/01

International application No.

PCT/SE 01/00753

Patent document cited in search report				Publication date		Patent family member(s)		Publication date	
WO	0012489	A1	09/03/00	AU	5892399	A	21/03/00		
				EP	1109790	A	27/06/01		
				SE	9802937	D	00/00/00		
<hr/>									
WO	9804135	A1	05/02/98	AU	711736	B	21/10/99		
				AU	4067997	A	20/02/98		
				BR	9710793	A	17/08/99		
				CN	1226803	A	25/08/99		
				CZ	9900321	A	16/06/99		
				EP	0915856	A	19/05/99		
				HU	0000063	A	29/01/01		
				IL	128308	D	00/00/00		
				JP	2000516925	T	19/12/00		
				NO	990428	A	29/01/99		
				PL	331385	A	05/07/99		
				US	5869509	A	09/02/99		
				US	6077861	A	20/06/00		
				ZA	9706554	A	25/01/99		
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